

### **REMARKS/ARGUMENTS**

As an initial matter, Applicants wish to thank the Examiner for withdrawing the objections to the specification, the rejections of the claims under 35 U.S.C. §112, second paragraph, the rejection of the claims as being obvious over U.S. Patent No. 5,004,605 in combination with U.S. Patent No. 6,525,102, and the obviousness-type double-patenting rejection of the claims over U.S. Patent No. 6,887,462.

Claims 1-26 are pending in the application and all claims stand finally rejected. Reconsideration of these claims is respectfully requested in view of the submission of the Terminal Disclaimer filed concurrently herewith and further in view of the arguments provided herein below. This Terminal Disclaimer and these arguments were not previously presented as Applicants' earnestly believed the prior claim amendments and arguments of record overcame the Examiner's objections to the claims.

The Examiner's comments in the outstanding final Office Action are addressed below in the order set forth therein.

#### **The Rejections of the Claims under 35 U.S.C. §103 Should Be Withdrawn**

Claims 1-26 stand rejected under 35 U.S.C. §103(a) over U.S. Patent No. 5,004,605 (Hershenson *et al.*) in view of *The Merck Index* (1983), p. 121, col. 2. This rejection is respectfully traversed.

Independent claims 1, 9, 15, and 20, and claims directly or indirectly dependent therefrom, recite stabilized HSA-free pharmaceutical compositions comprising substantially monomeric interferon-beta (IFN- $\beta$ ) or biologically active variant thereof solubilized in a low-ionic-strength formulation having an ionic strength that is not greater than about 20 mM. These compositions have a pH of about 3.0 to about 5.0, plus or minus 0.5 units, and further comprise trehalose. Applicants respectfully submit that these compositions, and the methods for their preparation, are not taught or suggested by the Hershenson *et al.* patent, alone or in combination with the teachings of *The Merck Index*.

Applicants remind the Examiner that the presently claimed invention is directed to pharmaceutical compositions comprising IFN- $\beta$  or biologically active variant thereof solubilized in a low-ionic-strength formulation. This formulation must meet two requirements: 1) it must contain a buffer in an amount sufficient to maintain the pH of the composition within the specified pH range; and 2) it must have a final ionic strength that is not greater than about 20 mM. Thus, when considering the teachings of the prior art, **both** of these claim elements must be taken into consideration, not just the amount of buffer present. In that regard, Applicants note that the compositions taught in the Hershenson *et al.* patent **do not meet the limitations required by both of these claim elements**, even if modified by substituting aspartic acid for those buffers taught by this cited patent, based on its pKa properties as taught by *The Merck Index*.

The Examiner correctly states that **Applicants** have calculated the ionic strength of the IFN- $\beta$  composition taught in Example 1 of the Hershenson *et al.* patent to be [at least] 44.23 mM (Office Action mailed September 14, 2007, at bottom of page 3). However, the Examiner then notes that the Hershenson *et al.* patent teaches a composition comprising IFN- $\beta$  and a phosphate buffer at a concentration of about 10 mM to about 25 mM (pointing to column 4, lines 58-59, and claim 10 of this patent), and then states, "It is also noted that the *ionic strength taught by the patent* (emphasis added) need not be the preferred embodiment in order to be obvious over the instant claims" (Office Action, at page 3, last two lines, continuing through page 4, line 3). Applicants respectfully submit that the Examiner has mischaracterized the teachings of the Hershenson *et al.* patent. In fact, where the compositions of this cited patent have a pH of 2-4 and comprise a phosphate buffer at a concentration of about 10 mM to about 25 mM, there is no requirement whatsoever that the compositions meet the second claim limitation, i.e., that they have a final ionic strength of not greater than about 20 mM. The Hershenson *et al.* patent fails to teach or even suggest this critical aspect of Applicants' claimed invention.

Rather, the Hershenson *et al.* patent teaches IFN- $\beta$  compositions having **buffer concentrations** as disclosed in column 4, lines 56-59, not IFN- $\beta$  compositions having a **final ionic strength**, as taught by Applicants and as required by Applicants' claimed invention. In

arguing the distinction between Applicants' claimed invention and the prior art, its is Applicants who have attempted to calculate the ionic strength of the composition actually prepared in Example 1 of the Hershenson *et al.* patent, in order to establish the non-obviousness of the presently claimed compositions. Furthermore, *The Merck Index* also fails to teach or suggest this critical aspect of Applicants' claimed invention, and thus cannot be combined with the teachings of the Hershenson *et al.* patent to arrive at Applicants' claimed invention.

As for the Examiner's reliance on *In Re Aller* (220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)) and *Peterson* (315 F.3d 1330, 65 USPQ2d 1382) at page 4 of the Office Action to assert that differences in concentration will not support the patentability of subject matter encompassed by the prior art without evidence of criticality of the recited concentration, Applicants respectfully submit that the presently claimed invention is not the reflection of mere optimization of the concentration of the buffers taught by the Hershenson *et al.* patent. As Applicants have explained above, any comparison between the teachings of the prior art and the presently claimed compositions must take final ionic strength of the IFN- $\beta$  compositions into consideration, not just their buffer concentration. The Hershenson *et al.* patent has no requirement whatsoever with respect to the final ionic strength of the IFN- $\beta$  compositions taught therein, and this missing claim element is not taught or suggested by the secondary reference, *The Merck Index*.

Applicants respectfully submit that it is improper for the Examiner to read Applicants' claim limitation into the compositions described by the Hershenson *et al.* patent, alone or in combination with the pKa properties of aspartic acid as taught by *The Merck Index*, in order to assert that the presently claimed invention is obvious over the teachings of the cited prior art. As the Examiner is aware, hindsight reconstruction is an impermissible standard upon which to make an obviousness determination. *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992) (ruling that it is impermissible to use the claimed invention as an instruction manual or template to piece together the teachings of the prior art to render it obvious).

Applicants once again wish to draw the Examiner's attention to the prosecution record for copending and commonly owned U.S. Patent Application No. 11/062,146 (the '146

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application), for which the Notice of Allowance was mailed out January 10, 2008. This application is related to the present application by virtue of their common parent application, U.S. Application No. 10/035,397, now U.S. Patent No. 6,887,462. In the Office Action dated June 26, 2007, in the '146 application, Examiner Christina M. Borgeest provided comments of record with regard to Hershenson *et al.* (U.S. Patent No. 5,004,605) and *The Merck Index* stating:

The Applicants overcame a rejection under 35 U.S.C. 103(a) of claims in U.S. Application No. 10/035,397 (now U.S. Patent No. 6,887,462) by showing evidence (in the form of calculations) that the final ionic strength of the composition taught by the Hershenson patent is at least 44.23 mM. While the ionic strength taught by the patent need not be the preferred embodiment in order to anticipate the instant claims, what is disclosed in column 4 are buffer concentrations, not final ionic strengths. Hershenson does not teach final ionic strength as calculated by Applicant (see Examiner's Reasons for Allowance 9 December 2004).

Office Action dated June 26, 2007, at page 6, lines 14-21, U.S. Patent Application No. 11/062,146.

Examiner Borgeest's comments with respect to these two references are in keeping with the reasons for allowance that were provided by Examiner Janet L. Andres, who handled prosecution of the parent application, 10/035,397. Thus, Hershenson *et al.* teach IFN- $\beta$  compositions having buffer concentrations as disclosed in column 4 of the Hershenson *et al.* patent, not IFN- $\beta$  compositions having a final ionic strength, as taught by Applicants and as required by Applicants' claimed invention. For all of the reasons of record in the parent and copending application, as well as the above-identified application, Hershenson *et al.* and *The Merck Index* do not teach or suggest Applicants' claimed IFN- $\beta$  compositions.

As the Examiner is well aware, a *prima facie* case of obviousness under 35 U.S.C. § 103(a) requires that the combination of references places the claimed subject matter in the public domain prior to Applicants' date of invention. See *In re Zenitz*, 333 F.2d 924, 142 USPQ 158 (C.C.P.A. 1964). Thus, establishing a *prima facie* case of obvious requires that the cited references can be combined such that each and every element of the claimed invention is taught,

explicitly or implicitly, by the references and that a reasonable expectation of success exists in such a combination. In the instant case, neither of the cited references discloses, explicitly or implicitly, an IFN- $\beta$  composition formulated in the manner set forth in Applicants' claimed invention, wherein the final ionic-strength of the formulation is not greater than about 20 mM. The disclosures of the Hershenson *et al.* patent and *The Merck Index* simply cannot be combined to arrive at the claimed invention. *The Merck Index* does not cure the deficiencies of the Hershenson *et al.* patent. As such, the claims are not obvious in view of these two cited references, and the rejection of the claims under 35 U.S.C. § 103(a) should be withdrawn.

The Non-Statutory Obviousness-Type Double-Patenting Rejection Should Be Withdrawn

Claims 1-26 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 5, 7-20, and 22 of copending U.S. Application No. 11/062,146 (the '146 application). As Applicants have indicated above, the '146 application has been allowed, and it is anticipated that the '146 application will grant prior to the above-referenced application. A terminal disclaimer in compliance with 37 C.F.R. §1.321(c) is filed concurrently herewith. In view of this submission, Applicants respectfully submit that this rejection is now overcome.

**CONCLUSION**

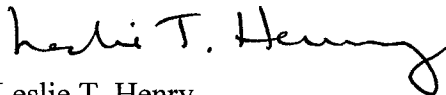
In view of the foregoing remarks and the Terminal Disclaimer filed concurrently herewith, Applicants respectfully submit that the obviousness-type double-patenting rejection and the rejection of the claims under 35 U.S.C. §103 are overcome. Accordingly, Applicants submit that this application is now in condition for allowance. Early notice to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby

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petitioned under 37 CFR §1.136(a), and any fee required therefore is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



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